

REMARKS

In an Office Action dated November 21, 2007, claims 2, 3, 5-7, 9-11, 14-17, 19, and 22-23, all of the claims pending in the above-identified patent application, were rejected. By this Amendment, claim 26 has been amended. Support for this amendment can be found throughout the specification and claims as originally filed. Specifically, support can be found, *inter alia*, at paragraph [0030] of the specification. The present Amendment does not introduce any new matter and thus its entry is respectfully requested. In view of the above claim amendment, Applicants' previous submissions, and the following remarks, Applicants respectfully request reconsideration of this application and allowance of the claims, as amended.

Claims 26-33 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Office Action, claim 26 is vague and indefinite because the only active process step recited in the claim is "providing" a nerve regeneration tube, while the body of the claim recites inherent properties of the nerve regeneration tube. The Office Action asserted that more individual active process steps must be recited in the claim to clearly define a method of reconnecting nerve ends.

In response, without conceding the correctness of the opinion expressed in the Office Action, but to expedite allowance of the application, Applicants have amended claim 26. Applicants believe this amendment fully overcomes the rejection and therefore respectfully request the rejection's reconsideration and withdrawal.

Claims 2-3, 5-6, 9-11, 14-17, 19, 22-30, and 32-33 have been rejected under 35 USC § 103(a) as allegedly being unpatentable over Geistlich et al. US Patent No. 5,837,278 (Geistlich

'278), in view of Stensaas et al. U.S. Patent No. 4,778,467 and further in view of Shimizu U.S. Patent No. 6,090,117. Claims 2-3, 5-7, 9-11, 14-17, 19, and 22-23 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Geistlich, et al. in view of Stensaas et al., in view of Shimizu, and further in view of Humes (U.S. Patent No. 5,429,938). The full rationale for these rejections appears at pages 3-7 of the Office Action. Insofar as these rejections could apply to the claims, as amended, they are respectfully traversed.

The present claims are directed to a nerve regeneration tube for reconnecting nerve ends, a method for producing such a tube, and a method of reconnecting nerve ends utilizing such a tube. The tube is resorbable and has a resorbable sidewall formed with collagen sheet material having a compact smooth outer barrier surface, and a soft fibrous inner surface opposite the smooth barrier surface. The tube has a compact smooth outer barrier surface formed with the compact smooth outer barrier surface of the collagen sheet material so as to inhibit cell adhesion thereon and to act as a barrier to prevent passage of cells therethrough. The tube further has a soft fibrous inner surface for promoting nerve growth, the soft fibrous inner surface of the tube being formed with the soft fibrous inner surface of the collagen sheet material. The tube has an inner diameter of about 0.5 – 5 mm, and has opposite tube ends, within which tube ends, during use, are nerve ends for reconnection of the nerve ends, wherein the nerve regeneration tube avoids formation of scar tissue which impairs nerve healing.

In traversing the rejection, Applicants first direct attention to the Rule 132 Declaration of Dr. Myron Spector and the accompanying remarks presented in the response filed October 22, 2007. As noted previously, Dr. Spector has been a Professor of Orthopedic Surgery at Harvard Medical School since 1993, and has conducted research on nerve regeneration tubes for over a decade. The

Declaration included both remarks and data providing evidence of unexpected results over the prior art.

Specifically, as indicated in Dr. Spector's Declaration, the surface configuration of tubes defined by the present claims provides such tubes with unexpected properties which could not have been predicted based upon the prior art. As indicated in Applicants' previous response, in early studies in which Dr. Spector participated, comparisons were made between certain collagen nerve regeneration tubes ("the Integra tubes") and silicone nerve regeneration tubes. These studies (reported in exhibits B and C of the Declaration) showed that the silicone tubes resulted in substantially greater build-up of fibrous scar tissue within the tubes, as compared to the Integra collagen tubes, with the Exhibit C study indicating that the silicone tubes resulted in formation of a fibrous capsule 10 times thicker than in the Integra collagen tubes. As explained previously, the problem with such fibrous build-up is that this fibrous tissue contains contractile fibroblasts (myofibroblasts) which cause the contracture of the fibrous layer. The contracting fibrous cuff interferes with the elongation of axons through the tube, and thus interferes with nerve regeneration. As noted, although Dr. Spector did not recognize the significance at the time, the silicone tubes have a smoother inner surface than the Integra collagen tubes. As stated in the Declaration, Dr. Spector's subsequent research and analysis indicates the thickness of the fibrous scar which forms along the inner surface of the tube is related to the topography of the surface, with smoother surfaces favoring the formation of a thicker scar layer with a great number of contractile cells.

With respect to the cited art, as also indicated in Dr. Spector's Declaration, the Shimizu patent discloses 3-layer tubes which have smooth collagen or gelatin inner surfaces. Shimizu discloses from column 6, line 48 to column 7, line 50 thereof, formation of a 3-layer collagen tube.

A central collagen layer 21 initially is formed on a Teflon rod. This central collagen layer 21 is compressed into a high density, fine fibrous collagen layer, which necessarily and inherently imparts layer 21 with a smooth interior surface, according to Dr. Spector. After compression, the central layer 21 is removed from the Teflon rod, and the central layer 21 is repeatedly dipped into a hydrochloric acid solution containing collagen, to deposit collagen hydrochloric acid solution layers 22 and 23 on the inner and outer surfaces of the compressed collagen layer 21. According to Dr. Spector, the repeated dipping and drying procedure into collagen hydrochloric acid solution necessarily and inherently forms smooth amorphous inner and outer surface layers 22 and 23 on the compressed central layer 21 of the tube. The same result will necessarily and inherently be obtained if gelatin instead of collagen is utilized for the inner and outer surface layers. Under no conditions disclosed in Shimizu will a soft fibrous inner surface be formed.

As indicated in Dr. Spector's Declaration, based on Dr. Spector's studies and experience, the smooth inner surface that will be produced according to the methods of Shimizu will promote formation of a thick layer of fibrous scar tissue on the inner smooth surface of the tube, containing contractile fibroblasts (myofibroblasts) which cause contracture of the fibrous layer and interference with nerve regeneration.

As also indicated in Dr. Spector's Declaration, the Geistlich et al. patent discloses a resorbable collagen membrane which is surgically inserted around the periphery of a wound cavity to facilitate, e.g., bone regeneration. In view of this reference, when combined with the other applied references, persons of ordinary skill in the art could not have predicted the unexpected results which have been achieved with the present invention, as outlined below.

Attached to Dr. Spector's Declaration as Exhibit D was a summary of a study that Dr. Spector was involved in, and which was presented at the 2007 Society for Biomaterials meeting. The Exhibit D study compares results achieved in five groups of animals (Groups I-V) in a rat spinal cord model for nerve regeneration. The study included testing of the collagen tubes (Groups III and IV) which Dr. Spector and his co-workers fabricated by freeze drying Type I microfibrillar collagen from bovine tendon from Integra, after slurry injection of the collagen over a glass rod mandrel. These tubes do not have a soft fibrous inner surface.

As indicated in Dr. Spector's Declaration, the Exhibit D study included testing of BioGide® collagen membrane (Group V) from Geistlich Biomaterials, Wolhusen, Switzerland. This BioGide® collagen membrane material corresponds exactly to the BioGide® collagen sheet material exemplified in the present application and usable in accordance with the present claims. The BioGide® membrane sheet material utilized in Group V of the Exhibit D study has a compact smooth outer barrier surface and a soft fibrous inner surface. In Group V of the Exhibit D study, the tube was formed by wrapping BioGide® membrane sheet material around stump ends of severed spinal nerves, so as to form a nerve regeneration tube as set forth in the present claims, with the soft fibrous surface oriented inwardly toward the severed nerve tissue to form the inner surface of the tube.

As indicated in Dr. Spector's Declaration, in the Exhibit D study, the Group V animals with tubes formed of Geistlich BioGide® membrane material having a smooth outer surface and a soft fibrous inner surface, unpredictably had the highest number of axons in the center of the nerve defect, see, Figure 1 in Exhibit D.

As indicated in Dr. Spector's Declaration, in the Exhibit D study, the only difference between the Group V animals and the Group IV animals was the structure of the tubular material surrounding the severed nerve tissue. The "dorsal barrier" mentioned in the Exhibit D study refers to a collagen membrane draped over the implant site to assist in preventing overlying tissue (e.g., muscle) from collapsing into the nerve defect.

As indicated in Dr. Spector's Declaration, taking into consideration the differences in the tube structure alone, between the Group V and Group IV animals, persons of ordinary skill in the art could not have predicted that the presently claimed invention, utilizing the collagen membrane material of Geistlich et al. U.S. Patent No. 5,837,278 (Group V), could result in the unexpectedly highest number of center nerve axons among the test animals, as compared to collagen tubes without a soft fibrous inner surface (the Group IV tubes).

As indicated in Dr. Spector's Declaration, with reference to Exhibit E attached thereto, Fig. 1 thereof shows a cross-section through the BioGide® collagen membrane material with the compact smooth barrier side at the top, and the soft fibrous side at the bottom. As shown in Fig. 2 of Exhibit E, entubulation of a gap in a rat nerve (spinal cord) with BioGide® demonstrated the absence of a thick fibrous scar on the inner surface of the tube, and demonstrated the ingrowth of cells and tissue into the soft fibrous surface. Based on the prior art, persons of ordinary skill in the art could not have predicted the absence of a thick fibrous scar on the inner surface of a tube according to the present invention, in conjunction with ingrowth of cells and tissues into the soft fibrous inner surface of the tube.

Moreover, as also indicated in Dr. Spector's Declaration, the Humes reference cited in the Office Action cannot be combined with Geistlich et al. and Shimizu to render the present claims

obvious. Humes does not even relate to nerve regeneration tubes, but instead is directed toward a renal tubule tissue system wherein adult kidney cells are cultured in a medium which may contain Type I collagen and/or Type IV collagen. Humes cannot be combined with the other applied references to render obvious, or make predictable, the unexpected results achieved with the present invention. Therefore, for at least the reasons reiterated above, the invention is not obvious over the combination of reference teachings suggested in the Office Action.

Nevertheless, Applicants provide the following additional comments, in further support of the rejection's traversal. In that regard, Applicants note the comments set forth in the Office Action (pages 5-6) in response to Applicants' previously filed Amendment and Declaration. For convenience, these comments are reproduced in full below:

Applicant's arguments filed 10/22/07 have been fully considered but they are not persuasive. Both the declaration of Spector and Applicant's arguments are drawn to the making of a neural regeneration tube as described by Shimizu. Both the declaration and the arguments assert that if one uses the procedures of Shimizu, a three layer collagen tube is formed with a compressed smooth collagen interior surface, and not the fibrous interior surface as recited in the instant claims. However, the instant rejection is drawn to the use of the single sheet collagen material as a first part (the '278 patent), the forming of said single sheet collagen into a neural regeneration tube as taught by Stensaas (not Shimizu) by, for example, simply rolling the sheet into a tube and fastening the leading surfaces together (e.g. around a nerve) as a second part, and then the remaining claim limitations are taught by Shimizu for the advantages set forth above as the third part of the rejection. Because the single collagen sheet material of the '278 patent already possesses a smooth and a fibrous side, the fabrication procedures of Shimizu are not required nor are they used in the formulation of the rejection. (See November 21, 2007 Office Action, paragraph bridging pages 5-6).

Applicants believe that these comments do not accurately or fully represent the positions set forth in Applicants' previously submitted response and Declaration, nor do they provide sufficient or proper reasoning to support the obviousness rejections. In particular, the comments make no

mention of Applicants' presentation of unexpected results, which was a key focus of both the response and Declaration. As the Office is aware, such evidence, when presented, *must* be considered. In this case, the Office Action has simply restated the position that the rejection is based on a combination of references, without addressing the submitted evidence. While Applicants have pointed out previously, and above, that combining the references as the Office Action has done does not support the obviousness rejection, Applicants also importantly provided data showing that Applicants' invention yielded unexpected results over the art. The Office apparently has not considered this evidence, including, for example, the unexpected absence of a thick fibrous scar on the inner surface of a tube according to the present invention, and an unexpected ingrowth of cells and tissues into the soft inner surface of the tube. Through this evidence, Applicants have demonstrated unexpected results over the prior art. In doing so, Applicants respectfully remind the Office that "[a]pplicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." (See MPEP §716.02(e)). By simply reiterating the combination of cited reference teachings, what the Office Action *at best* can be said to have done is compared the Applicants' results not with existing prior art, but with a nerve regeneration tube that only results from the Office Action's suggested combination of teachings. Such an analysis is simply not proper, as the above noted section of the MPEP clearly indicates, when it states (citing *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966)):

Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 "would be requiring comparison of the results of the invention with the results of the invention." 357 F.2d at 422, 148 USPQ at 714. (MPEP §716.02(e)).

In the present case, the Office has failed to adequately and properly consider the evidence presented by the Applicants in support of the patentability of the claimed invention. Accordingly, for at least the reasons presented above, Applicants respectfully submit that the Office Action's rejections of the claims under 35 U.S.C. §103 are improper and should be withdrawn.

Applicants believe that the present Amendment fully addresses the concerns as set forth in the November 21, 2007 Office Action and that the application is in condition for allowance. Reconsideration of the instant application and an early notice of allowance are therefore requested. The Examiner is invited to telephone the undersigned if it will expedite allowance of the application.

Respectfully submitted,

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